REVIEW

Diagnosis and management of adult onset Still's disease

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Background: Adult onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown aetiology that is responsible for a significant proportion of cases of fever of unknown origin and can also have serious musculoskeletal sequelae.
Objective: To assess and synthesise the evidence for optimal diagnosis and management of AOSD.
Methods: The key terms, *adult onset Still's disease, AOSD, adult Still's disease, ASD, Still's disease* were used to search Medline (1966–2005) and PubMed (1966–2005) for all available articles in the English language. Clinically relevant articles were subsequently selected. Bibliographies, textbooks, and websites of recent rheumatology conferences were also assessed.
Results: Data on diagnosis and treatment of AOSD are limited in the medical literature and consist mainly of case reports, small series, and modest scale retrospective studies. Diagnosis is clinical and requires exclusion of infectious, neoplastic, and other autoimmune diseases. Laboratory tests are non-specific and reflect heightened immunological activity. Treatment comprises non-steroidal anti-inflammatory drugs, corticosteroids, immunosuppressive drugs (methotrexate, leflunomide, gold, azathioprine, ciclosporin A, cyclophosphamide), and intravenous gammaglobulin. The recent successful application of biological agents (anti-tumour necrosis factor, anti-interleukin (IL)1, anti-IL6), often in combination with traditional immunosuppressive drugs, has been very promising.
Conclusions: AOSD often poses a diagnostic and therapeutic challenge and clinical guidelines are lacking. The emergence of validated diagnostic criteria, discovery of better serological markers, and the application of new biological agents may all provide the clinician with significant tools for the diagnosis and management of this complex systemic disorder.

Adult onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown aetiology, characterised by quotidian or double-quotidian spiking fevers with an evanescent rash, arthritis, and multiorgan involvement. It owes its name to George Still who published in 1897 his monograph, *On a form of chronic joint disease in children,* describing 22 children with signs and symptoms of the disease entity currently known as systemic onset juvenile idiopathic arthritis. In 1971, Eric Bywaters described 14 adults with similar presentation with paediatric Still's disease, convincingly establishing the new disease entity.[1] However, the first description of an *adult* patient with signs and symptoms of AOSD, erroneously labelled rheumatoid arthritis, was published in the *Lancet* in 1896, one year before George Still's monograph.[2] Since then multiple reports of fever of unknown origin or ''rheumatoid arthritis'', which we would call AOSD, have appeared. In the French and German literature occasional reports of AOSD are found, then called ''subsepsis allergica'' or ''Wissler's syndrome'' and later the ''Wissler-Fanconi syndrome''.[3]

METHODS

We searched Medline and PubMed (1966–2005) using the key terms: a*dult onset Still's disease*, *AOSD*, a*dult Still's disease, ASD, Still's disease*, for all available articles in the English language, using the filters ''human'' and ''adult''. Reference lists of identified trials, review articles, and papers proposing diagnostic criteria were reviewed. In addition, textbook chapters (both printed and electronic) were assessed to identify additional relevant information. Websites of recent rheumatology conferences (including those of the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR)) were searched for recent studies presented but not yet published. About 200 references in the English language were initially retrieved based on their clinical relevance; the reference list was subsequently modified during the peer review process, on the basis of comments from the reviewers, to include 107 papers. No randomised controlled trials were identified, which could be explained by the rarity of the disease. The existing body of clinical literature consists of case reports, small series, and modest scale retrospective studies.

EPIDEMIOLOGY

AOSD is rare, not readily diagnosed, and currently there is no consensus on its incidence and prevalence in different populations. Based on the larger reviews from the 1980s it appears that it occurs world wide and affects women slightly more often than men. The disease characteristically affects younger people, with three quarters of the patients reporting disease onset between 16 and 35 years of age.[4 5] In a Dutch retrospective review of 45 patients, 60% of the patients were women and the median age of onset was 25 years (range 16–65), with 27% of the patients showing the first symptom after the age of 35.[6] In a retrospective study of 62 patients from western France, the incidence was estimated to be 0.16 per 100 000 inhabitants with a bimodal peak at ages 15–25 and 36–46 without a sex bias.[7] However, an epidemiological

Abbreviations: ANA, antinuclear antibodies; AOSD, adult onset Still's disease; ASD, adult Still's disease; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IFNγ, interferon γ; IL, interleukin; JIA, juvenile idiopathic arthritis; IVIG, intravenous gammaglobulin; LFTs, liver function tests; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RF, rheumatoid factor; TNFα, tumour necrosis factor α; TRAPS, TNF receptor associated periodic syndrome; WBC, white blood cell

survey from Japan reported that 67% of the cases presented after the age of 35, the majority (65–70%) being women.[8] AOSD affects all ages, and several cases have been reported after the age of 60.[4 9] Stress has been suggested as an important risk factor for all ages.[10]

PATHOGENESIS

The aetiology of AOSD, like most rheumatic diseases, is currently unknown. A genetic component has been suggested by many studies, linking the disease with a number of HLA antigens. In a retrospective review of 62 patients from Canada, 55 underwent immunogenetic studies and HLA-B17, B18, B35, and DR2 were associated with a relative risk ranging from 2.1 to 2.9.[11] However, other studies did not confirm these findings and other associations were reported, including HLA-B14 and DR7, or Bw35 and Cw4, or DR4 and Dw6.[4] The hypothesis that AOSD may be a reactive syndrome, where various infectious agents may act as disease triggers in a genetically predisposed host, has been very popular, and a variety of organisms have been proposed. Some clinical manifestations of AOSD are reminiscent of those seen in self limited viral infections. Viruses such as rubella, mumps, echovirus 7, cytomegalovirus, Epstein-Barr virus, parainfluenza, Coxsackievirus B4, adenovirus, influenza A, human herpes virus 6, parvovirus B19, hepatitis B, and hepatitis C have all been implicated in case reports and small series.[4 12–14] Other studies have proposed microbial triggers, including *Mycoplasma pneumoniae, Chlamydia pneumoniae, Yersinia enterocolitica* 3 and 9, *Brucella abortus*, and *Borrelia burgdoferi*, in the pathogenesis of AOSD.[4 15 16] The observation that many different infectious agents may act as disease triggers, suggests a similarity with reactive arthritis.[4]

> ''The hypothesis that infectious agents may trigger AOSD suggests a similarity with reactive arthritis''

More recently, it has been suggested that alterations in cytokine production have an important pathophysiological role in AOSD. A predominance of Th1 cytokines was shown in the peripheral blood and tissues of patients with active untreated AOSD.[17] The Th1 immune response is characterised by increased production of interleukin (IL)2, interferon γ (IFNγ), and tumour necrosis factor α (TNFα) cytokines that steer B cells toward IgG2a production, activate macrophages and NK cells, and promote cell mediated immunity. Serum levels of IL6, TNFα, and INFγ were significantly increased in 12 patients with active AOSD when compared with controls.[18] IL18 is another proinflammatory cytokine closely related to the AOSD pathogenesis, as it is overproduced in the acute phase of the disease and is believed to be the cytokine initiating the inflammatory cascade that includes IFNγ, IL6, and TNFα.[19] Genetic polymorphisms of the human IL18 gene have been described and the S01/S01 diplotype conferred disease susceptibility in a Japanese study.[20] In another Japanese study, serum levels of soluble IL2 receptors, IL4, and IL18 correlated with chronic articular AOSD activity, while IFNγ and IL8 levels were persistently raised, even in disease remission. TNFα, soluble TNF receptor 2, and IL18 were also persistently raised in both the systemic and the chronic articular forms of AOSD.[21] There seems to be an increased activation of γδ T cells of the $V\gamma_9/V\delta_2$ type in active *v* inactive AOSD.[22]

CLINICAL MANIFESTATIONS

AOSD typically manifests as a triad of symptoms that include high-spiking fevers, a characteristic rash, and arthritis/arthralgias. Fever generally exceeds 39°C and is transient, lasting typically under 4 hours, and is most commonly quotidian or double quotidian in pattern, with the highest temperatures seen in the late afternoon or early evening.[3 6] Fever can herald the onset of other manifestations as well, with serositis, sore throat, myalgias, and arthralgias described. Overall incidence of fever across five of the largest retrospective studies was 95.7% (table 1).[6 11 14 23 24]

The typical rash is an evanescent, salmon-pink, maculopapular eruption, predominantly found on the proximal limbs and trunk, with rare involvement of the face and distal limbs. Often accompanied by fever, the rash can be mildly pruritic, and confused with a drug allergy. A Koebner phenomenon has been described.[11] Histology shows perivascular inflammation of the superficial dermis with invasion of lymphocytes and histiocytes, and immunohistochemistry sometimes positive for complement and immunoglobulin.[11 23] Incidence ranges from 51% to 87%, with an average of 72.7%.[6 11 14 23 24] In three cases,[25–27] a vasculitic purpuric rash was also described and an association with mixed cryoglobulinaemia was suggested in one of them.[25]

Arthralgia and arthritis are found in the majority of patients with AOSD, with incidences ranging from 64% to 100%.[6 11 14 24] Joints affected most frequently are the knees, wrists, and ankles, although involvement of the elbow, shoulder, proximal and distal interphalangeal joints, metacarpophalangeal and metatarsophalangeal joints, temporomandibular joints, and hip have been described as well.[11 23] In particular, carpal and pericapitate abnormalities are typically higher than in cases of rheumatoid arthritis, offering a means to clinically differentiate the two entities. Of note, changes in the wrist typically present 6 months after disease onset, with progressive joint space narrowing in a pericapitate or carpometacarpal distribution, and ankylosis developing after 1.5–3 years.[1 28 29] The pattern of arthritis is typically symmetric, with most patients developing polyarthritis and joint pain associated with fever spikes. Such complaints are often

Table 1 AOSD clinical manifestations in the largest series (percentage of patients)

	Study (No of patients)							
Manifestations	Wouters (28)[6]	Masson (65)[23]	Ohta (90)[14]	Pouchot (62)[11]	Fujii (systemic) (18)[21]	Fujii (chronic articular) (17)[21]	Fautrel (72)[24]	Andres (17)[32]
Sore throat	68	68	70	92	67	71	38	35
Myalgia	75	62	56	84	61	12		
Fever	100	94	100	100			85	82
Arthritis	68	69	72	94	89	100		
Arthralgia		100	100	100	11	0	64	53
Lymphadenopathy	54	48	69	74	56	47	32	35
Rash	54	85	87	87	94	88	51	76
Splenomegaly	14	22	65	55	56	29	32	
Pleuritis	25	15	12	53				
Pericarditis	25	23	10	37			15	

Table 2 Articular manifestations in chronic articular AOSD (% patients)

	Study (No of patients)	
Manifestations in:	Pouchot (62)[11]	Masson (65)[23]
Knee	82	69
Wrist	73	67
Ankle	55	38
PIP	47	44
Elbow	44	29
Shoulder	40	24
MCP	35	42
MTP	18	11
Hip	11	7
DIP	10	9
PIP	3	0
TMJ	3	4

Results from two large series.
MCP, metacarpophalangeal; MTP, metatarsophalangeal;; DIP, distal interphalangeal;; PIP, proximal interphalangeal; TMJ, temporomandibular joint.

short lived, resolving as the fever diminishes. Joint aspiration fluid often discloses marked leucocytosis, with a neutrophilic predominance (table 2).[11 23]

''The majority of patients with AOSD have arthralgias and arthritis''

Myalgia is another common manifestation, with incidence ranging from 56% to 84%.[6 11 14 23] Distribution remains generalised, and most often appears with exacerbations of fever. Inflammatory myopathy is rarely found, although a number of case reports have described an increase of muscle enzymes in patients' sera.[30 31]

Liver abnormalities, predominantly hepatomegaly and abnormalities in liver biochemistry, are present in approximately 50–75% of patients, but it has been suggested that liver dysfunction secondary to non-steroidal anti-inflammatory drug (NSAID) use may be a significant cofactor.[6 24 32] AOSD can present as pseudo-angiocholitis.[33] Jaundice and acute hepatitis leading to hepatic failure and requiring liver transplantation remain exceedingly rare.[34 35]

Less common manifestations include pleuritis (26.4%), pericarditis (23.8%), and splenomegaly (43.9%).[6 11 14 23 24 32 36] Additional cardiac complications that have been noted to a lesser extent include tamponade and myocarditis.[37] Pulmonary manifestations include fibrosis, pleural effusions, and, rarely, adult respiratory distress syndrome.[38–40] Renal disease is rare and can manifest as interstitial nephritis, subacute glomerulitis, renal amyloidosis and, the more recently described, collapsing glomerulopathy. The last of these is a relatively newly recognised entity, originally described in HIV patients (HIV associated nephropathy) in the 1970s, but is also seen in non-HIV patients and is characterised by heavy proteinuria and rapidly progressive renal failure with poor outcome.[41–44] Haematological complications (thrombotic thrombocytopenic purpura, pure red cell aplasia), and neurological complications (cranial nerve palsies, seizures, aseptic meningoencephalitis, Miller-Fisher syndrome) are rarer still.[11 14 43–47]

LABORATORY AND RADIOGRAPHIC FINDINGS

The diagnosis of AOSD remains a clinical one. Unlike other systemic rheumatic diseases, it is not associated with rheumatoid factor (RF) or antinuclear antibody (ANA) positivity, and this fact has been used in various sets of criteria used to define the disease. In fact, the laboratory profile of the disease is a reflection of the systemic inflammation and cytokine cascade present. The erythrocyte sedimentation rate (ESR) was raised in virtually all patients in three of the largest series described.[6 11 48] C reactive protein (CRP) may also be found to be raised.[49] Common haematological abnormalities include leucocytosis, which often accompanies increased disease activity, anaemia, and thrombocytosis.[5 6 11] Leucocytosis is the result of a striking neutrophilia that is probably secondary to bone marrow granulocyte hyperplasia.[11 50] In a series of 62 patients, 50% of the patients had peripheral leucocyte counts $>15\times10^9$/l, and 37% had white blood cell (WBC) counts $>20\times10^9$ cells/l.[11] Anaemia of chronic disease is seen with active disease, which often returns to normal when the disease subsides.[11] Reactive thrombocytosis is common. Pancytopenia should alert the physician to the presence of haemophagocytic syndrome, which has been reported in AOSD and necessitates prompt immunosuppressive treatment.[50] Coagulation abnormalities are rare and consist of prolongations of partial thromboplastin time or prothrombin time; cases of disseminated intravascular coagulation have been described that have led to death.[11]

Increases in lactic dehydrogenase, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, and bilirubin can be seen in up to three quarters of patients and frequently occur concomitantly with fever and exacerbations of arthritis.[4] Liver biopsy typically shows mild periportal inflammation with monocyte infiltration.[11]

Recently, serum ferritin and glycosylated ferritin have received a lot of attention as diagnostic and disease activity markers. Ferritin, an acute phase reactant, is intimately involved in inflammatory processes, including the mechanisms underlying oxidative stress. Inflammation is associated with increased production of ferritin by the histiocyte-macrophage system and/or increased release from damaged hepatocytes. Several cytokines—mainly, IL1β, IL18, TNFα, and IL6, seem to drive the increased production of ferritin.[51] Ferritin levels in AOSD are usually higher than those found in patients with other autoimmune or inflammatory diseases. In most studies, a threshold for serum ferritin levels of 1000 ng/ml, five times the upper limits of normal (40–200 ng/ml), has been used to suggest AOSD.[51] Very high levels ranging from 4000 ng/ml to 30 000 ng/ml are not uncommon, and even extreme levels as high as 250 000 ng/ml have been recorded.[52] Furthermore, serum ferritin levels correlate with disease activity and often normalise when the disease goes into remission.[53–55] The validity of hyperferritinaemia as a diagnostic tool was evaluated in a retrospective French study[56] with 49 patients, where a fivefold increase in serum ferritin had 80% sensitivity and 41% specificity and, similarly, in a Japanese study[57] with 82% sensitivity and 46% specificity. The usefulness of serum ferritin is limited by the fact that very high levels can also be seen in other diseases, such as liver disease (haemochromatosis, Gaucher's disease), infections (sepsis, HIV), malignancies (leukaemia, lymphomas), and, especially, in the haemophagocytic syndrome.[51 52]

''The glycosylated fraction of ferritin is a more specific marker of AOSD than ferritin itself''

A more specific diagnostic marker than ferritin may be its glycosylated fraction. In healthy subjects, 50–80% of ferritin is glycosylated, a process that provides protection from proteolytic enzymes. In inflammatory diseases, saturation of glycosylation mechanisms causes the glycosylated fraction to drop to 20–50%. This phenomenon is particularly prevalent in AOSD, where the glycosylation of ferritin is often <20%. Interestingly, defective glycosylation of other acute phase reactants has been reported as well in AOSD. It has been suggested that, in addition to the saturation of the

glycosylation mechanisms, other more disease-specific mechanisms might be in place, such as decreased clearance of non-glycosylated proteins by the histiocyte-macrophage system.[51] Glycosylated ferritin cannot be used to monitor disease activity or response to treatment, as it remains low for many months after the disease goes into remission.[58] When combined with a fivefold serum rise in ferritin, the sensitivity fell to 43% and specificity rose to 93%.[56] Better diagnostic tests are clearly needed and new immunological tests, such as IL18, may prove useful in the near future for diagnosis as well as monitoring disease activity and response to treatment.[19 59] Until the development of these tests, clinicians will continue to use the currently available tests: complete blood count and differential, ESR, CRP, ANA, and RF (both negative), liver function tests (LFTs) and albumin, ferritin, and glycosylated ferritin (if available).

Radiographs during the initial acute phase of the disease are not usually very helpful in establishing the diagnosis, being either normal or showing soft tissue swelling, joint effusion, or mild periarticular demineralisation.[11] Radionuclide bone scan and gadolinium enhanced magnetic resonance imaging were assessed in small series and may prove to be more sensitive imaging modalities for early diagnosis and successful treatment in follow up.[16] In one study, 41% of patients developed a distinctive pattern of intercarpal and carpometacarpal joint space narrowing (bilateral in 69%), that led to pericapitate ankylosis in 25% of the cases.[11] Other investigators have also reported a tendency for distal interphalangeal, intertarsal, and cervical zygapophyseal ankylosis.[52] Patients who have the chronic articular disease pattern often present with joint erosions. A French group[60] reported frequent severe involvement of the hip requiring total hip replacement, a finding that was not replicated in a Japanese study.[36] Figure 1 shows radiographic manifestations of AOSD arthritis.

Currently, no consensus has been reached as to whether AOSD and its juvenile counterpart (systemic onset juvenile idiopathic arthritis (JIA),[61] formerly known as paediatric Still's disease) represent the same clinical continuum rather than being distinct entities. The diagnosis of systemic onset JIA is clinical and based on the presence of characteristic disease manifestations, distinct from other forms of JIA, and an age of onset <16 years, while diagnosis of AOSD requires an age of onset >18 years. Both entities share typical clinical features such as the abruptness of onset, the fever patterns, the transient nature of the rash, the almost equal female to male ratio, the arthritis, and the neutrophilia.[62] Furthermore, recent research has shown that a similar pattern of cytokines (IL6, IL18, TNFα) may be involved in the pathogenesis of both disorders. Despite those similarities, other studies have reported differences in levels of acute phase reactants (ferritin, chymotrypsin)[63] and, especially, prognosis. In children, systemic disease onset is typically between 3 and 5 years, and organ involvement is frequently present. Children severely affected by systemic onset JIA are at significant risk of lifelong disability and up to 50% develop a chronic, destructive polyarthritis 5–10 years after diagnosis [64 65] that often appears to be less responsive to treatment, even with anti-TNF treatment.[66 67]

DIAGNOSIS

The clinical presentation of AOSD is heterogeneous, and the spectrum of differential diagnoses is wide, including infectious, neoplastic, and autoimmune disorders, which should be ruled out before the diagnosis of AOSD can be made. Viral syndromes (for example, rubella, cytomegalovirus, Epstein-Barr virus, mumps, Coxsackievirus, adenovirus) can be excluded if the symptoms persist beyond 3 months. Surveys of infections, including cultures and serological tests, can be especially helpful early in the disease. Neoplastic disorders that can mimic AOSD include leukaemia, lymphoma, and angioblastic lymphadenopathy. However, the clinical presentation can differ substantially, with atypical rashes and/or isolated lymph node enlargement. The haematological profile can help to differentiate the disease entities, but sometimes bone marrow and/or lymph node biopsy may be needed.[52] Occasionally, the constellation of findings (fever, abdominal pain, and mesenteric lymphadenopathy) has led to exploratory laparotomy before the diagnosis of AOSD was entertained.[11] Conditions commonly confused with the AOSD include reactive arthritis and the other spondyloarthropathies, haemophagocytic syndrome, dermatomyositis, Kikuchi's syndrome, Sweet's syndrome, granulomatous disorders, and the vasculitides.[52 68]

Another category of syndromes that may mimic the clinical manifestations of AOSD are the periodic fever syndromes,

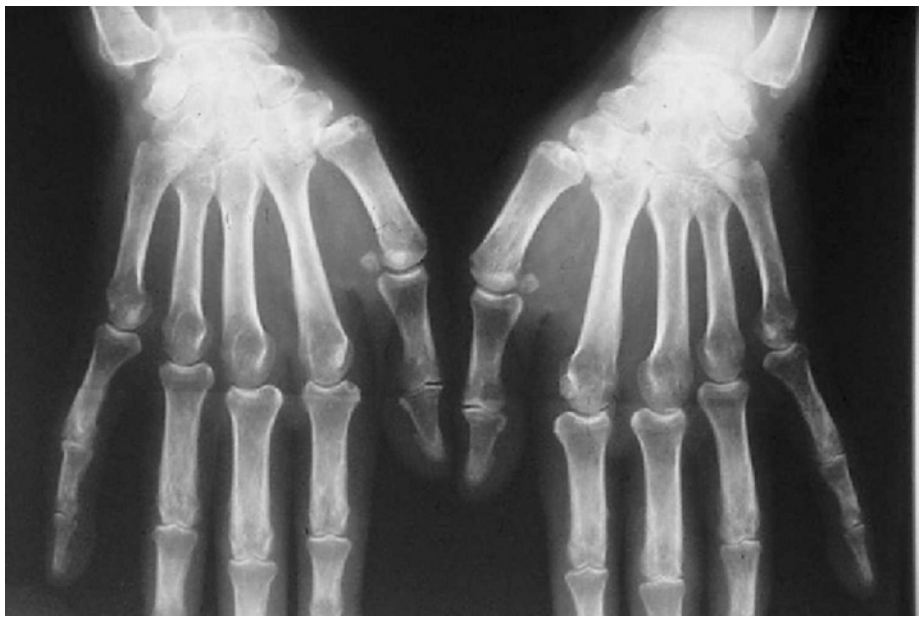

Figure 1 Patients with AOSD often develop a distinctive pattern of intercarpal and carpometacarpal joint space narrowing that can lead to pericapitate ankylosis. (Image reproduced with permission from http://www.cri-net.com, accessed 15 February 2006)

and in particular, in this age group, familial Mediterranean fever and TNF receptor associated periodic syndrome (TRAPS). Patients with familial Mediterranean fever often present with acute, self limited episodes of fever accompanied by signs of peritonitis, pleuritis, or acute synovitis, mainly of the knee, ankle, or hip. Erysipelas-like erythema can accompany the fever, which does not have the quotidian pattern of AOSD and usually lasts for 1–3 days. The disease often starts in childhood or early adolescence. A significant family history (including ethnic background) together with the distinct clinical characteristics and response to colchicine can direct the clinician towards the correct diagnosis, which can be verified, in many cases, with genetic analysis for the *MEFV* gene. TRAPS commonly starts in childhood and also has a strong familial distribution. Fever attacks last longer, 21 days on average, and are associated with ocular involvement and with a distinctive centrifugal, erythematous patch.[69]

Several sets of classification criteria have been published for AOSD. They have all been developed from retrospective data and classify criteria as major or minor. One study attempted to validate these classification criteria: Yamaguchi's criteria[57] were shown to be the most sensitive (93.5%), followed by Cush's[70] (80.6%) and Calabro's[71] (80.6%). As there was no control group, no validation of specificity was available.[72] More recently, a French group has proposed a new set of criteria that, unlike those previously described, does not contain exclusion criteria and takes into consideration the two new disease markers: serum ferritin and its glycosylated fraction. This set provided a sensitivity of 80.6% and a specificity of 98.5%, which remains to be validated in a different population before becoming widely accepted.[24] Table 3 compares the Yamaguchi criteria with the widely used Cush clinical criteria and the newly proposed criteria by Fautrel *et al*.[24]

COURSE AND PROGNOSIS

The clinical course can fall into three distinct patterns, with significant prognostic implications, each affecting about one third of patients with AOSD.[52 73]

- The *self limited* or *monocyclic* pattern is characterised by systemic symptoms (fever, rash, serositis, and organomegaly). Most patients achieve remission within 1 year (median time is 9 months) from the first and only disease episode.[6]
- The patients with the *intermittent* or *polycyclic systemic* pattern experience recurrent flares, with or without articular symptomatology. There is complete remission between the flares, that may be years apart and tend to be milder than the initial episode.[11]
- The *chronic articular* pattern is dominated by the articular manifestations that can be severe and lead to joint destruction. In one series, 67% of patients in this group required at least one total joint replacement after a median of 28 (13–60) months from disease onset.[6]

Patients with chronic articular disease generally have more disability and worse prognosis than patients with only systemic symptoms. Rash, polyarthritis, and root joint (shoulder, hip) involvement at disease onset, were predictors of a chronic articular pattern in one retrospective study.[11] Patients with systemic disease have a favourable prognosis, with only rare serious complications from the disease (pericarditis, tamponade, diffuse intravascular coagulation, amyloidosis, hepatic disease, and respiratory failure) or the treatment (infections, gastrointestinal bleeding, etc).[6]

TREATMENT

Treatment in AOSD has been exclusively empirical, with data on treatment efficacy extrapolated from case reports and small scale retrospective studies. These have been further confounded by frequently inconsistent treatment regimens and a proliferation of qualitative descriptions of the data. Although the low incidence of AOSD makes it difficult to carry out prospective, controlled treatment trials, higher standards of interpretation and presentation of existing retrospective data are needed.

The treatment of AOSD has centred around the use of NSAIDs, steroids, and antirheumatic agents to control fever,

Table 3 AOSD diagnostic criteria

Yamaguchi *et al*[57]	**Cush**[70]	**Fautrel** *et al*[24]
Major		
Arthralgia >2 weeks	(2 points)	Spiking fever ⩾39°
Fever >39°, intermittent, ⩾1 week	Quotidian fever >39°	Arthralgia
Typical rash	Still's (evanescent) rash	Transient erythema
WBC >10 000 (>80% granulocytes)	WBC >12.0+ESR >40 mm/1st h	Pharyngitis
	*N*egative RF and ANA	PMN ⩾80%
	Carpal ankylosis	Glycosylated ferritin ⩽20%
Minor		
Sore throat	(1 point)	
Lymphadenopathy and/or splenomegaly	Onset age <35 years	Maculopapular rash
LFT abnormal	Arthritis	Leucocytes $\geqslant 10\times10^9$/l
(-)ve ANA and RF	Prodromal sore throat	
	RES involvement or abnormal LFTs	
	Serositis	
	Cervical or tarsal ankylosis	
Diagnostic combination		
Exclusion criteria		
Infections	*Probable AOSD*: 10 points with 12 weeks' observation	4 major criteria or 3 major+2 minor
Malignancies	*Definite AOSD*: 10 points with 6 months' observation	
Rheumatic diseases		
Diagnosis		
5 criteria (at least 2 major)		

RES, reticuloendothelial system; PMN, polymorphonuclear cells.

arthritis, and systemic disease, beginning with the treatment of AOSD by Bywaters in 1971.[1] Evidence of the varying efficacies of these treatments in AOSD was later elucidated in several retrospective studies, including a multicentre study in France of 65 patients with AOSD.[74] Initial treatment of these patients comprised aspirin in 23 patients, NSAIDs in 21 patients, and glucocorticoids in 21 patients. Disease in about 12% of patients was controlled with NSAID monotherapy, compared with 7% and 15% in earlier studies.[11 14] Eighty eight per cent of patients required prednisone in addition to NSAIDs at some point, with 46% of patients requiring maintenance prednisone treatment. A subsequent study emphasised the relative inefficacy of salicylates and suggested indometacin and naproxen as more useful class representatives.[6]

As NSAID monotherapy is effective in controlling disease in only 7–15% of patients, most patients are treated with steroids at some point in their disease course, with responses ranging from 76% to 95%.[6 70 74 75] The efficacy of glucocorticoids was demonstrated by Wouters *et al*, who showed that 16/21 (76%) patients responded favourably to glucocorticoids administered for the control of systemic and joint disease. However, eight of those receiving a maintenance dose of 10–15 mg/day prednisone for arthritic symptoms developed severe joint destruction despite steroid treatment.[6] In the study by Masson *et al*, maintenance prednisone treatment in addition to NSAID use was required in 30 patients (46%), with 57 patients (89%) requiring prednisone at some point during their disease.[74] Similar requirements for steroid use were found by Larson and Bywaters in 50%[3] and 54%[1] of their patient cohorts, respectively.

> ''Most patients with AOSD will need treatment with corticosteroids at some point in their disease course''

There seems to be an increasing need for steroid treatment based on the disease pattern. Prednisone was required for 57% of patients with self limited, 67% with intermittent, and 77% with chronic articular AOSD.[11] The usefulness of intravenous pulse methylprednisolone to treat disease refractory to oral prednisone and the availability of dexamethasone as a prednisone alternative have also been demonstrated in case reports and small series.[76 77] As a whole, studies indicate the need for steroid treatment in most patients with AOSD. Within this population, disease in the majority of patients is well controlled. Guidelines for the use of steroids are derived from their use in juvenile Still's disease. Large doses of prednisone should be limited to 6 months for the treatment of NSAID refractory systemic disease, presenting with persistent anaemia, pericarditis, serositis, and raised liver enzymes.[4 52]

The use of remittive drugs in AOSD is marked by an absence of prospective, clinically controlled trials, which has proved to be additionally problematic because of the unclear efficacy of antirheumatic drugs in anecdotal case studies and small scale retrospective studies. Broadly, these studies suggest that the use of antirheumatic drugs should be reserved for cases in which the combination of NSAIDs and steroids fails, or in which a reduction in the requirement for steroids is desired, either owing to lack of tolerance or adverse events. Antirheumatic agents that have been studied include ciclosporin A,[78] hydroxychloroquine, gold, penicillamine, azathioprine, cyclophosphamide, and methotrexate (MTX), with modest success and overall response across studies at approximately 40%.[9 14 70 79–81] In a study by Wouters *et al*, of 18 trials of antirheumatic drugs used in 13 patients with disease refractory to NSAIDs and corticosteroids, only eight (44%) proved clinically efficacious. The list of antirheumatic drugs used included hydroxychloroquine (0/3 respondents), gold (6/8 respondents), penicillamine (4/6 respondents), and azathioprine (0/1 respondents).[6]

Masson *et al* demonstrated that 22/65 (34%) patients required additional remittive treatment to maintain disease control, 20 (91%) of whom were concomitantly receiving prednisone.[74] Of the 13 patients receiving MTX as the remittive agent in that group, 11 (85%) were able to taper the prednisone dose. Similarly, Fautrel *et al*, in a study of 26 patients diagnosed with refractory AOSD, found that 23 (88%) patients responded to treatment with low dose MTX (11.5 (3.6) mg/wk), with 18/23 (78%) entering complete remission. In addition, daily prednisone intake decreased by 69%, and 11 (42%) of these 26 patients were able to discontinue prednisone altogether.[82] Polyarthritis was particularly susceptible to MTX treatment and resolved completely in many cases, while the effect of MTX on non-articular manifestations of AOSD was less well defined. Side effects of MTX treatment included mild rises in LFTs, gynecomastia, nausea and vomiting, and varicella zoster infection. Serious infections (*Legionella* pneumonitis and cerebral nocardiosis) occurred when higher doses of MTX (40 and 50 mg/day) were used.[83]

The use of intravenous gammaglobulin (IVIG) in AOSD has also been described in the treatment of flares and disease refractory to NSAIDs, with responses (13/15, cumulatively) seen at doses ranging from 0.4 to 2 g/kg/day for 2–5 days and remission lasting for 2–53 months.[84–86] Interestingly, IVIG may have a role in the induction of remission and control of early disease before the use of steroids, with Vignes *et al* demonstrating an absence of flares in 4/7 patients after the cessation of IVIG to the end of the study period; three of those responders were eventually able to discontinue the use of NSAIDs.[86] All seven patients were relatively newly diagnosed, with a mean (SD) duration of AOSD before the first IVIG infusion of 32.5 (22) days.[86] The results must be interpreted with caution, as the group with early disease may include patients who will go into spontaneous remission and the efficacy of any therapeutic agent can be overestimated. Whether remission can be induced in patients diagnosed with chronic AOSD remains to be studied. Additionally, IVIG in combination with mycophenolate mofetil was used successfully in a case of severe collapsing glomerulopathy associated with AOSD.[41]

TNF blocking agents have also been employed in uncontrolled studies.[87–89] Etanercept in conjunction with MTX and corticosteroids was used successfully by Asherson and Pascoe in a single patient when multiple immunosuppressive drugs and plasmapheresis had failed.[27] In an open label trial of etanercept (25 mg twice weekly, with an increase to three times a week at 8 weeks if no improvement was seen) in a cohort of 12 patients, addition of the soluble TNF receptor to the pre-study regimens of prednisone, MTX, and NSAIDs led to a 67% improvement in the number of tender joints and a 63% improvement in the number of swollen joints at the end of the 6 month trial.[88] Furthermore, etanercept use in a patient with Still's disease and nephrotic syndrome due to renal AA amyloidosis, a rare complication of the disease, resulted in amelioration of proteinuria.[90] Side effects associated with etanercept treatment in AOSD include injection site reactions,[88] paradoxical disease flares,[88] cutaneous eruption,[88] infectious complications (sinusitis,[88] listeriosis,[91] skin abcesses[92]), upper respiratory tract illness,[88] and diarrhoea.[88]

Use of infliximab, the monoclonal chimeric anti-TNFα antibody, has also been reported in various open label trials to be effective in AOSD.[93] In a study of three patients with chronic AOSD unresponsive to conventional treatment with prednisone and MTX, addition of infliximab (3 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter) led to decreases in ESR, CRP, serum ferritin, and fever and improvements in

both the patient's and physician's global assessment by week 2, which extended to the end of the trial at week 50. Clinical improvement also allowed for a gradual decrease in prednisone dose, from 15–30 mg/day to 7–12 mg/day.[89]

In a Greek case series, four patients refractory to high doses of corticosteroids and MTX responded favourably to treatment with infliximab 3 mg/kg. All four patients went into remission soon after their first infusion, and serum inflammation indices closely followed the clinical improvement. Systemic corticosteroids were quickly tapered off and long term remission was sustained.[94]

The efficacy of infliximab in MTX+corticosteroid resistant AOSD was also reported by Huffstutter and Sienknecht (two patients),[95] Bonilla Hernan *et al* (two patients),[96] Caramaschi *et al* (one patient),[97] and Dilhuydy *et al* (one patient).[98] Infliximab at a dose of 5 mg/kg was found to be effective in a patient with early AOSD who was steroid resistant and ineligible for MTX treatment.[99] A European series of eight patients (three male, five female) diagnosed with AOSD, attempted to evaluate the long term outcome of patients treated with infliximab (3–5 mg/kg) after their treatment with corticosteroids and traditional disease modifying antirheumatic drugs had failed. Seven out of eight patients had a positive response with rapid improvement in both clinical and serological response and five (four in the acute and one in the chronic articular phase) went into long term remission, even after discontinuation of treatment. The responders who did not go into long term remission included a patient with intermediate disease who was switched to etanercept after experiencing an infusion reaction and a second patient with chronic articular disease who required continuous treatment with infliximab to control the severe arthritis. The one patient who did not respond to infliximab (and subsequently neither to etanercept nor to adalimumab) had chronic articular disease.[100]

A larger observational study (20 patients) reported the French experience with the use of TNF inhibitors in corticosteroid (and MTX) resistant AOSD.[92] The disease manifestation was systemic in five and polyarticular in 15 patients. Ten patients received only infliximab, five only etanercept, and five were treated with both drugs consecutively. After a mean (SD) follow up of 13 (14) months, complete remission was seen in five patients (one treated with etanercept and four treated with infliximab). Most patients (16/25 treatments) achieved a partial remission: 7/10 were receiving etanercept and 9/15 infliximab. Although the study design does not allow for definitive comparisons between the two agents (infliximab *v* etanercept), there appeared to be a trend towards differential efficacy of anti-TNF agents. Infliximab induced four complete and long-lasting remissions, while etanercept produced one, albeit on a patient treated concomitantly with 80 mg of prednisolone/day and 100 mg azathioprine/day. Four treatment failures occurred, equally divided among both treatments and they all occurred in patients with childhood onset of disease, probably representing cases of systemic onset JIA (or juvenile Still's disease), a condition that has been shown to be less responsive to anti-TNF treatment.[66 67]

The use of infliximab in AOSD has been associated with rare, albeit occasionally serious, side effects, including infusion reactions,[97 100] cutaneous eruptions,[89 99] recurrent bronchitis and pneumonia,[92] pneumonitis,[101] heart failure,[92] blurry vision,[92] and fulminant hepatitis in a patient with concomitant hepatitis B.[102]

IL6 is thought to be an important proinflammatory cytokine in the disease pathogenesis and a promising target, especially with the development of anti-IL6 treatments. One case report demonstrated a marked decrease in CRP, defervescence, and improvements in arthralgia in AOSD refractory to MTX, ciclosporin A, and prednisolone, after the administration of anti-human IL6 monoclonal antibody (MRA).[103]

Most recently, IL1 blockade has emerged as a possible new therapeutic option. Firstly, it was reported to be effective in a patient with refractory AOSD, for whom multiple disease modifying antirheumatic drugs (MTX, sulfasalazine, ciclosporin A), IVIG, and TNF inhibitors had failed to produce sustained remission and prolonged corticosteroids administration had resulted in serious side effects. When anakinra 100 mg subcutaneously/day was added to MTX 25 mg/week,

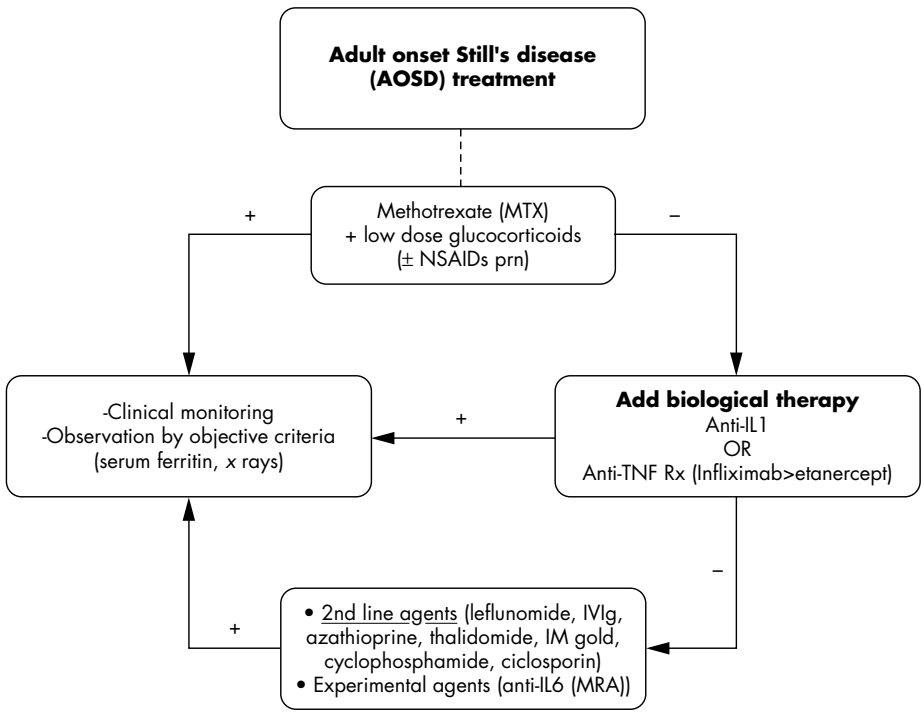

Figure 2 Therapeutic algorithm for AOSD.

a moderate dose of prednisolone (20 mg/day), and naproxen, the patient reported a decrease of arthritic and systemic symptoms within weeks, paralleled by a normalisation of serum acute phase reactants. The patient achieved a prolonged remission when given MTX+anakinra.[104] In the 2004 EULAR meeting, a report by Haraoui *et al* described the successful treatment of three patients with refractory chronic AOSD with daily subcutaneous anakinra 100 mg. Clinical improvement was seen within days of starting treatment and eventually allowed the prednisone dose to be tapered significantly.[105] Also in this meeting, Aelion *et al* reported the successful outcome of daily anakinra 100 mg subcutaneously in two patients with persistent AOSD. Clinical improvement was again seen in days in one patient and within a few weeks in the other. The first patient was reported to be in complete remission when receiving anakinra alone, with normalised laboratory values. The other patient was weaned off corticosteroids and remained stable with a combined regimen of anakinra and oral MTX (10 mg/week).[106] More recently, another study also showed the efficacy of anakinra in the treatment of four patients with AOSD who were refractory to treatment with corticosteroids and MTX. Interestingly, two of the four patients had been unsuccessfully treated earlier with etanercept, which had been added to the standard regimen of MTX+corticosteroids. In all four cases, the patients responded quickly to anakinra; within days symptoms resolved and laboratory values (WBC count, ferritin, CRP) normalised.

It is woth mentioning that when anakinra was withheld on two occasions, the disease relapsed within days, with reappearance of fever, arthritis, and rash paralleled by a rise in laboratory markers (WBC count, ferritin, CRP). Both patients responded quickly when anakinra was restarted. Remission was prolonged and allowed for tapering of the prednisone dose and eventual discontinuation in three out of four patients.[107] Multicentre, controlled studies are needed to validate these early, open label studies.

Figure 2 shows in a schematic form, our recommendations for a treatment strategy, taking into consideration the recent data on biological agents.

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